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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,706	10/20/2003	Joseph Loscalzo	102258.170 US2	2830

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WILMERHALE/NITROMED
1875 PENNSYLVANIA AVE, NW
WASHINGTON, DC 20006

EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,706	LOSCALZO ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response and amendments filed 17 October 2006 to Office Action mailed 17 July 2006 is acknowledged and entered.

2. The Art Unit Location for your application under prosecution at the United States Patent and Trademark Office (i.e., USPTO) has been changed to Art Unit 1657. To aid in correlating any papers for this application (i.e., 10/687,706), all further correspondence regarding this application should be directed to Examiner Kailash C. Srivastava in Art Unit 1657.

CLAIMS STATUS

3. Claims14-15 and 26-169 have been cancelled.

4. Claims 1-13 and 16-22 have been amended.

5. Claims 1-13 and 16-25 are pending and are examined on merits.

Information Disclosure Statement

6. For the record, on page 1 of the Information Disclosure Statement filed 17 October 2006, next to the heading, "Application Number:" a statement has been made "NOT YET ASSIGNED". On the accompanying sheets 1-5 of FORM 1449A/PTO the application number (i.e., 10/679,257) is clearly mentioned. Appropriate correction/clarification for this inconsistency is in order.

7. The Information Disclosure Statement (i.e., IDS) concurrently filed with the response filed 17 October 2006 to Office Action mailed 17 July 2006 is acknowledged, has been made of record, considered and form 1449A/PTO submitted 17 October 2006 has been initialed and is enclosed.

Claim Rejections Under 35 U.S.C. § 103(a)

8. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C.§ 103(a).

10. Claims 1-13 and 16-25 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Birch et al (U.S. Patent 5,627,191) in view of Cohn (U.S. Patent 4,868, 179) and further in view of Chobanian et al (U. S. Patent 5,645,839).

In response to rejection to claims 1-13 and 16-25 under 35 U.S.C. § 103 (a) cited *supra* in Office Action mailed 17 July 2006, applicants argue that these references, alone or in combination do not teach the present invention and therefore do not render the instantly claimed invention unpatentable/obvious. Applicants argue that Birch et al. or Cohn do not teach any motivation to combine hydralazine hydrochloride and/or isosorbide dinitrate/ mononitrate with an oral sustained release formulation and further argue that Chobanian et al. do not teach combining any of hydrazine hydrochloride and/or isosorbide dinitrate/ mononitrate with a oral sustained release formulation. Applicants also argue that Cohn teaches a method to treat a vascular disease through administering isosorbide dinitrate, hydrazine hydrochloride and some other components.

Applicants are absolutely correct in arguing that each one of the references cited *supra;* individually do not make the instantly claimed invention obvious. The claimed invention, however, is drawn to a sustained release oral formulation (i.e., composition) comprising each one of isosorbide dinitrate and hydrazine hydrochloride and another component and a method to treat a nitric oxide insufficiency mediated vascular disease, wherein said disease is a cardiovascular disease among a laundry list of diseases and said cardiovascular disease is hypertension among another laundry list of diseases. Applicants, in their remarks filed 17 October 2006 admit on record that Birch et al. teach a method to treat cardiovascular disease via administering a

composition comprising hydrazine hydrochloride (See Remarks Page 5, Line 28; Page 6, Lines 7 and17). As discussed above, hypertension is a cardiovascular disease. Cohn clearly teaches a composition comprising each of the instantly claimed components, viz. isosorbide dinitrate and hydrazine hydrochloride and further teaches a method to treat, congestive heart failure with said composition (See Cohn, Column 2, Lines 26-60, Column 3, Lines 1-35 and Abstract). Congestive heart failure is one of the disease as mentioned in the laundry list of diseases claimed in Claim 25 of instantly claimed invention. Chobanian et al. teach a composition comprising an angiotensin inhibitor and at least one nitric oxide stimulator (Column 7, Lines 53-55), wherein said nitric oxide stimulator is isosorbide dinitrate (Column 8, Lines 51-54 and 52-63) and those compounds are in form of coated tablets or capsules (Column 5, Lines 35-37). Since sustained release preparation by definition are "A way of formulating a medicine so that it is released into the body steadily, over a long period of time, thus reducing the dosing frequency (See www.ardana.co.uk/glossary.html), Chobanian et al. explicitly teach a composition comprising isosorbide dinitrate and angiotensin inhibitor and intrinsically said composition is a sustain release oral composition. Chobanian et al. further teach that said composition is useful in treating cardiovascular pathologies (i.e., cardiovascular diseases). Thus, Chobanian et al. teach a composition that is a sustained release oral formulation to treat a vascular disease as is claimed in the instant invention. Additionally, the claimed invention is obvious over the combined teachings from each one of Birch et al., Cohn and Chobanian et al. for the reasons of record (See Office Action mailed 17 July 2006, Pages 3-5, item 15) and as discussed above.

Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art at the time the invention was made. See *In re Keller* 642. F. 2d 413, 208 USPQ 871 (CCPA 1981). Note that although each of the Examiner-cited references by themselves may not teach every component in the same order or manner as claimed in the claims under prosecution in the instant application, these references are not relied upon exclusively but in combination. Furthermore, the 35 U.S.C. §103 statute does not require that the prior art identically disclose or describe Applicants' invention but rather that no patent should be obtained if the subject matter

as a whole would have been obvious to persons having ordinary skill in this art at the time the invention was made. In this case, given the teachings from each one of Birch et al, Cohn and Chobanian et al., the claimed invention would have been obvious to a person of ordinary skill at the time the claimed invention was made.

Applicants' arguments cited *supra* have been fully and carefully considered, but are not persuasive for the reasons of record at Pages 3-4, item 13 of the Office Action mailed 17 July 2006 and further for the reasons explained in the preceding paragraph.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, those reasons are cited at pages 4-5, item 15 of the Office Action mailed 13 July 2006 and for additional reasons as discussed *supra*. Furthermore, a rejection under 35 U.S.C. § 103 (a) based upon the combination of references is not deficient solely because the references are combined based upon a reason or technical consideration which is different from that which resulted in the claimed invention.(*Ex parte Raychem Corp*, 17 U.S.P.Q. 2d 1417).

In response to applicants' arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

CONCLUSION

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. For the aforementioned reasons, no claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1657
(571) 272-0923

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1657

March 18, 2007